UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/598,356	08/11/2008	Kerstin Menander	SOBL.P0051US/11003930	2981

32425 7590 12/09/2010

FULBRIGHT & JAWORSKI L.L.P.
600 CONGRESS AVE.
SUITE 2400
AUSTIN, TX 78701

EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	**PAPER NUMBER**
1632	

NOTIFICATION DATE	DELIVERY MODE
12/09/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

aopatent@fulbright.com

Office Action Summary	Application No.	Applicant(s)	
	10/598,356	MENANDER ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *2,11,13,14,16-19,21-24,27 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-10,12,15,20,25,26,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 April 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/23/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application 10/598,356 is a 371 of PCT/US2005/006108 filed on 02/24/2005 which claims benefit of 60/547,145 filed on 02/24/2004.

Election/Restriction

Applicant's election without traverse of Group III, claims 1, **3**-26, 29, and 30, drawn to a method of treating a subject with recurrent cancer comprising: (a) selecting a patient based on (i) prior treatment of cancer with a *radiotherapy*, and (ii) recurrence of cancer subsequent to said treatment, (b) administering to said subject an expression construct comprising a nucleic acid segment encoding p53, said segment under the control of a promoter active in a cancer cell of said subject, said expression construct expressing p53 in said cancer cell; and (c) subsequent to step (b), administering to said subject a *chemotherapy*, whereby said expression construct sensitizes said cancer cell to said chemotherapy, thereby treating said cancer, in the reply filed on 07/06/2010 is acknowledged.

Upon further consideration, it is noted that dependent claim 2 recites "wherein said first radio- or chemotherapy and said second radio- or chemotherapy are *the same*" is encompassed by Groups I and Group II inventions, but is <u>not</u> encompassed by Groups III-VI inventions documented in the restriction mailed on 03/04/2010.

In response to requirement for election of species, Applicant elected the following species elections without traverse: **(i)** carboplatin (recited in claim 5), **(ii)** x-rays (recited in claim 7), **(iii)** head & neck cancer (recite din claim 8), **(iv)** an adenoviral construct (recited in claim 10), **(v)** viral (recited in claim 9), (vi) replication defective (recited in claim 12), **(vii)** CMV IE

promoter (recited in claim 15), **(viii)** about 14 (recited in claim 20), **(ix)** intratumoral (recited in claim 30), in the reply filed on 10/07/2010 is acknowledged. Applicant states that Applicants have therefore withdrawn claims 11, 13, 14, 16-19 and 21-24 as drawn to non-elected inventions, subject to rejoinder.

Upon searches and further consideration, **(i)** listed above the species election between "carboplatin" and "cisplatin" recited in claim 5 is *withdrawn*; and **(iii)** listed above the species election between "head and neck cancer" and "lung cancer" recited in claim 8 is *withdrawn*.

Claims 1-30 are pending. Claims 2, 11, 13, 14, 16-19, 21-24, 27, and 28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

Claims 1, 3-10, 12, 15, 20, 25-26, 29 and 30 are currently under examination to the extent of elected species as stated above.

Claim Objections

1. Claim 1 and its dependent claims 3-10, 12, 15, 20, 25-26, 29 and 30 are objected to for being drawn to a non-elected invention. Specifically, Applicants have elected Group III, claims 1-26, 29, and 30, drawn to a method of treating a subject with recurrent cancer comprising: (a) selecting a patient based on (i) prior treatment of cancer with a *radiotherapy*, and (ii) recurrence of cancer subsequent to said treatment, (b) administering to said subject an expression construct comprising a nucleic acid segment encoding p53, said segment under the control of a promoter active in a cancer cell of said subject, said expression construct expressing p53 in said cancer cell; and (c) subsequent to step (b), administering to said subject a *chemotherapy*, whereby said

expression construct sensitizes said cancer cell to said chemotherapy, thereby treating said cancer; and as such, claim 1 and dependent claims 3-10, 12, 15, 20, 25-26, 29 and 30 are examined only to the extent that they read on the limitation "(i) a prior treatment of cancer with a *radiotherapy*" and the limitation "subsequent to step (b), administering to said subject a *chemotherapy*" recited in claim 1. Applicants are required to delete the non-elected subject matter from the instant claims [i.e. non-elected subject matter being surgery and chemotherapy recited in step (a) (i) of claim 1, and radiotherapy recited in step (c) of claim 1; and amending claims 3, 4, and 6 to be directed to first treatment being radiotherapy and second treatment being chemotherapy].

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1, 3-10, 12, 15, 20, 25, 26, 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Roth et al.** (US Patent 6,069,134, issued 05/30/2000) in view of **Roth et al.** (Roth et al., Retrovirus-mediated wild-type p53 gene transfer to tumors of patients with lung cancer, *Nat. Med.* 2(9):985-991, 1996; this reference has been cited as reference C10 in the IDS filed by Applicant on 02/23/2007), and **Staar et al.** (Staar et al., Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy--results of a

multicentric randomized German trial in advanced head-and-neck cancer, *Int J Radiat Oncol Biol Phys* 51(2):569, 2001).

Claims 1, 3, 4, and 6 are directed to a method of treating a subject with recurrent cancer comprising: (a) selecting a patient based on (i) prior treatment of cancer with a radiotherapy, and (ii) recurrence of cancer subsequent to said treatment, (b) administering to said subject an expression construct comprising a nucleic acid segment encoding p53, said segment under the control of a promoter active in a cancer cell of said subject, said expression construct expressing p53 in said cancer cell; and (c) subsequent to step (b), administering to said subject a chemotherapy, whereby said expression construct sensitizes said cancer cell to said chemotherapy, thereby treating said cancer.

Claim 5 is directed to the method of claim 4, wherein said chemotherapy comprises administration of carboplatin.

Claim 7 is directed to the method of claim 5, wherein said radiotherapy is x-rays.

Claim 8 is directed to the method of claim 1, wherein said cancer is head & neck cancer.

Claim 9 is directed to the method of claim 1, wherein said expression construct is a viral expression construct.

Claim 10 is directed to the method of claim 9, wherein said viral expression construct is an adenoviral construct.

Claim 12 is directed to the method of claim 10, wherein said viral expression construct is a replication- defective virus.

Claim 15 is directed to the method of claim 1, wherein said promoter is CMV IE.

Claim 20 is directed to the method of claim 1, wherein the time period between steps (b) and (c) is about 14 days.

Claim 25 is directed to the method of claim 1, wherein recurrence is recurrence at a primary tumor site.

Claim 26 is directed to the method of claim 1, wherein recurrence is recurrence at a metastatic site.

Claim 29 is directed to the method of claim 1, wherein administering in step (b) is intratumoral.

Claim 30 is directed to the method of claim 1, wherein administering in step (c) is intratumoral.

Claim interpretations: The chemotherapy drug "carboplatinum" recited in claim 5 is interpreted as "carboplatin" as indicated by Applicant's election of species filed on 10/07/2010, and the spelling of "carboplatin" is consistent with the disclosure by Staar et al. cited in the 103 rejection.

With regard to the limitation of steps (b) and (c) of claim 1, and the limitations of claims 3, 4, and 6, **Roth et al.** (2000) teaches the use of tumor suppressor genes in combination with a DNA damaging agent or factor for use in killing cells, and in particular cancerous cells (See abstract and bridging paragraph, columns 4-5, Roth et al.). A tumor suppressor gene, p53, was delivered via a recombinant *adenovirus*-mediated gene transfer both *in vitro* and *in vivo*, in combination with a chemotherapeutic agent (See abstract and lines 25-35 and column 8, Roth et al.). Treated cells underwent apoptosis with specific DNA fragmentation (See abstract and lines 51-61, col. 29, Roth et al.). Direct injection of the p53-adenovirus construct into tumors subcutaneously, *followed by* intraperitoneal administration of a DNA damaging agent, cisplatin, induced massive apoptotic destruction of the tumors (See abstract and bridging paragraph, columns 7-8, Roth et al.). Roth et al. teaches a method of killing a tumor cell in a tumor of a human cancer patient by expressing functionally active p53 from a DNA construct (claims 1 and 3, Roth et al.), and the expression of p53 results in apoptotic destruction of the tumors (abstract and lines51-53, column 29)

With regard to chemotherapy drug recited in claim 5 and route of administration of p53 construct and chemotherapy drug recited in claims 19 and 20, Roth et al. teaches *direct injection of the p53-adenovirus construct into tumors* subcutaneously, followed by intraperitoneal administration of a DNA damaging agent, cisplatin, induced massive apoptotic destruction of the tumors (See abstract and bridging paragraph, columns 7-8, Roth et al.). Roth et al. teaches p53 and cisplatin treatment and direct *intratumoral* injection of Ad-p53 (See lines 52-58, column 19, Roth et al., 2000). Roth et al. teaches that DNA damaging agent cisplatin is not absorbed orally and must therefore be delivered via injection intravenously, subcutaneously, *intratumorally* or intraperitoneally (See lines 5-7, column 19).

With regard to the limitation of claim 7, Roth et al. teaches the treatment method further comprise contacting tumor with DNA damaging agent (claim 42), comprises γ-irradiation, *X-ray*, UV-irradiation (See for instance, line 61 column 4).

With regard to the limitation of cancers recited in claim 8, Roth et al. (2000) teaches the tumors are either malignant or benign and comprise human breast cancer, lung cancer, sarcoma, melanoma, lymphoma, epithelial cancer carcinoma cancer (claims 30-39).

With regard to the limitations of claims 9, 10, 12, and 15, Roth et al. teaches the expression vector encoding p53 can be delivered by a variety of vectors including adenoviral vectors (claims 23-28, Roth et al.), *replication-deficient* wild-type p53 *adenovirus* (abstract, Roth et al.), adenovirus lacking E1 region (claims 52 and 53), with *CMV IE promoter* driving p53 expression (lines 53-61, column 6, claim 22).

With regard to the limitations of claims 25 and 26, Roth et al. teaches that p53 has an important role as a determinant of chemosensitivity in human lung cancer cells. A variety of

treatment protocols, including surgery, chemotherapy, and radiotherapy, have been tried for human NSCLC, but the long-term survival rate remains unsatisfactory. What is needed is a *combination therapy* that is used alone or as an effective adjuvant treatment to prevent local *recurrence following primary tumor resection* or as a treatment that could be given by intralesional injections in drug-resistant *primary, metastatic*, or locally recurrent lung cancer (See lines 21-30, column 3, Roth et al., 2000).

Roth et al. (2000) does not explicitly teach **(I)** step (a) selecting a patient based on (i) prior treatment of cancer with a radiotherapy, and (ii) recurrence of cancer subsequent to said treatment recited in claim 1, **(II)** carboplatinum" as a chemotherapy drug recited in claim 5, "head and neck cancer" recited in claim 8, and the limitation "wherein the time period between steps (b) and (c) is *about* 14 days" recited in claim 20.

(I) With regard to the limitation step "(a) selecting a patient based on (i) prior treatment of cancer with a radiotherapy, and (ii) recurrence of cancer subsequent to said treatment" recited in claim 1, **Roth et al. (1996)** teaches administration of viral vector containing the wild-type p53 gene into human non-small cell lung cancer. Nine patients whose conventional treatment failed were entered into clinical study (See abstract, Roth et al. 1996). Roth et al. teaches prior treatment of patient #1 to 9 and responses of treated lesion of these patients (See Table 1, page 986, provided below in this office action, Roth et al., 1996). For instance, the prior treatment of patient #5 include resection of solitary brain metastasis with *whole-brain radiation*, and the

response of treated lesion includes >50% regression of treated endobronchial tumor with viable tumor in pre-and post-treatment biopsies.

Table 1 Characteristics of patients and response to injections of retroviral vector ITRp53A

Pt no.	Sex	Age	Performance status (Zubrod)	Histologic	Prior treatment	Site of treatment	Route of treatment	Mutation (codon, base change, amino acid change)	Response of treated lesion (response duration in weeks)	Survival after treatment* (weeks)
1	M	60	1	squamous	drainage of pleural abscess, 30 Gy lung tumor, 13 Gy brachytherapy	left mainstem bronchus	bronchoscopic	138, CTC→CTG Leu→Val	viable tumor in pretreatment biopsy; no viable tumor at treated site by bronchoscopy, biopsy, and autopsy (17)	17
2	M	58	1	squamous	66 Gy lung tumor	right upper lobe	bronchoscopic	248, CGG→CTG Arg→Leu	viable tumor in pretreatment biopsy; no viable tumor in 6 posttreatment biopsies at 1 month (10)	22
3	M	61	1	large cell	surgical resection, 60 Gy post-op	right upper chest wall	percutaneous by CT	243, GGC→AGC Gly→Ser	stable by chest radiograph and CT scan (9); viable tumor in pretreatment biopsy; 3 posttreatment biopsies show no viable tumor	9
4	M	73	2	adenocarcinoma	vinblastine, mitomycin, 2 months	left anterior chest wall	percutaneous by fluoroscopy	249, AGG→ATG Arg→Met	inevaluable	3
5	M	56	2	adenocarcinoma	resection of solitary brain metastasis with whole-brain radiation, vinblastine, mitomycin, methotrexate, 6 months; paclitaxel, 3 months; 30 Gy to lung tumor	right upper lobe	bronchoscopic	269, frame-shift insertion	>50% regression of treated endobronchial tumor with viable tumor in pre- and posttreatment biopsies (4)	4
6	M	72	1	squamous	resection of brain metastasis with whole-brain radiation, paclitaxel, 3 months; 45 Gy to lung tumor 9 months before entry	right posterior chest wall	percutaneous by CT	157, GTC→TTC Val→Phe	progression by CT scan; viable tumor in pre- and posttreatment biopsies	13
7	M	57	1	large cell	cisplatin, VP-16, 5-FU, 6 months; surgical resection, 63 Gy post-op; docetaxel, 2 months	left adrenal metastasis	percutaneous by CT	135, TGC→TAC, Cys→Tyr	stable with increased lucency on CT scan suggestive of tumor necrosis and relief of flank pain (8); viable tumor in pre- and posttreatment biopsies	22
8	M	51	1	large cell	surgical resection; ifosfamide, mitomycin & cisplatin, 9 months; 59 Gy chest wall radiation 5 years before entry	left posterior chest wall	percutaneous by CT	150, ACA→ATA, Thr→Ile 157, GTC→TTC, Val→Phe 175, CGC→ AGC, Arg→Ser	stable (8); viable tumor in pre- and posttreatment biopsies	20
9	M	68	2	squamous	52 Gy lung tumor, 20 Gy right bronchus, and 6.7 Gy at 10 mm left bronchus	carina	bronchoscopic	143, TGC→TGA, Trp→stop	inevaluable	6

*All patients died from progression of untreated metastases or other complications.

With regard to **(II)** "carboplatinum" as a chemotherapy drug recited in claim 5, "head and neck cancer" recited in claim 8, **Staar et al.** teaches that radiation therapy (RT) and chemotherapy may be combined in several ways for treating *head-and-neck* cancer. The two treatments may be given simultaneously, *in alteration or* ***sequentially***. RT may be delivered with

a conventional fractionation or with an accelerated and/or hyperfractionated regimen. Early randomized trials with conventionally fractionated RT and concurrent single-agent chemotherapy with methotrexate, 5-FU, low-dose cisplatin, or mitomycin C revealed significant improvements in local control and/or survival. *Carboplatin* has radiosensitizing properties comparable to cisplatin; however, carboplatin can be administered *with minimal hydration, and causes less nausea* (See third paragraph, right column, page 1168, Staar et al., 2001).

With regard to **(II)** the limitation "wherein the time between steps (b) and (c) is *about* 14 days" recited in claim 20, **Staar et al.** teaches chemotherapy guidelines as follows: For patients in arm B, chemotherapy was performed in week one and five. 5-FU was given as continuous infusion (600 mg/m^2/day) and *carboplatin* as short-term infusion (70 mg/m^2) on *days 1-5 and 29-33*, starting before the first daily fraction. It was recommended to treat these patients on an in-patient basis (See left column, page 1164, Staar et al., 2001). It is noted that the primary reference Roth et al. (2000) teaches the protocol of direct injection of the p53-adenovirus construct into tumors subcutaneously, *followed by* administration of a DNA damaging agent, cisplatin, induced massive apoptotic destruction of the tumors (See abstract and bridging paragraph, columns 7-8, Roth et al.). The teachings of Staar regarding administration of carboplatin as short-term infusion (70 mg/m^2) on *days 1-5 and 29-33* indicates the second administration of carboplatin being after 14 days of first administration. Based on the variation of patients disclosed by Roth et al. (1996), the determination of the range of days subsequent to step (b) as recited in step (c) of claim 1 is a process of routine optimization of the protocols for cancer treatment of each patient/subject by the claimed methods. In this regard, Applicant attention is directed to MPEP 2144.05 cited below.

2144.05 [R-5] Obviousness of Ranges

See MPEP § 2131.03 for case law pertaining to rejections based on the anticipation of ranges under 35 U.S.C. 102 and 35 U.S.C. 102/103.

II. OPTIMIZATION OF RANGES

A. Optimization Within Prior Art Conditions or Through Routine Experimentation

Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

B. Only Result-Effective Variables Can Be Optimized

A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or

workable ranges of said variable might be characterized as routine experimentation. In re Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977) (The claimed wastewater treatment device had a tank volume to contractor area of 0.12 gal./sq. ft. The prior art did not recognize that treatment capacity is a function of the tank volume to contractor ratio, and therefore the parameter optimized was not recognized in the art to be a result-effective variable.). See also In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) (prior art suggested proportional balancing to achieve desired results in the formation of an alloy).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Roth et al. (2000) regarding the use of tumor suppressor genes in combination with a DNA damaging agent or factor for use in killing cells, and in particular cancerous cells, and direct injection of the p53-adenovirus construct into tumors subcutaneously, followed by administration of a DNA damaging agent, cisplatin, induced massive apoptotic destruction of the tumors with the teachings of (i) Roth et al. (1996) regarding nine patients whose conventional treatment failed were entered into clinical study, and for instance, the prior treatment of patient #5 include resection of solitary brain metastasis with whole-brain radiation, and the teachings of (ii) Staar et al. regarding guidance of chemotherapy of carboplatin as short-term infusion (70 mg/m^2) on days 1-5 and 29-33, starting before the first daily fraction, and radiation therapy (RT) and chemotherapy may be combined in several ways for treating head-and-neck cancer as the two treatments may be given simultaneously, in alteration or *sequentially,* to arrive the claimed methods recited in claimed 1, 3-10, 12, 15, 20, 25, 26, 29 and 30 of instant application.

One having ordinary skill in the art would have been motivated to combine the teachings of Roth et al. (2000) et al. with the teachings of Roth et al. (1996) and Staar et al. because Roth et al. (2000) teaches the framework of effective treatment of a cancer, for instance treatment of a lung cancer, by p53 gene therapy followed by chemotherapy which for instance uses chemotherapy drug cisplatin, whereas the teachings of Roth et al. (1996) et al. complement the teachings of Roth et al. (2000) by providing detailed characteristics of patients elected for clinical trial of lung cancer treatment by p53 gene therapy. The teachings by Staar et al. (2001) complement the teachings of Roth et al. (2000) by providing the chemotherapy guidelines for treating head and neck cancer using chemotherapy drug carboplatin.

There would have been a reasonable expectation of success given (i) the disclosure of a direct injection of the p53-adenovirus construct into tumors subcutaneously, followed by intraperitoneal administration of a DNA damaging agent, cisplatin, induced massive apoptotic destruction of the tumors, by the teachings of Roth et al. (2000) (See abstract and bridging paragraph, columns 7-8, Roth et al. 2000), and (ii) the demonstration of the characteristics of nine patients with lung cancer whose conventional treatment failed were entered into clinical study for lung cancer treatment via a viral vector mediated p53 gene therapy, by the teachings of Roth et al. (1996) (See abstract and Table 1, Roth et al. 1996), and (iii) the demonstration of chemotherapy guidelines regarding *carboplatin* as short-term infusion (70 mg/m^2) on days 1-5 and 29-33, for treatment of head and neck cancer, and radiation therapy (RT) and chemotherapy may be combined in sequential order for treating head-and-neck cancer, by the teachings Staar et al. (2001).

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

The Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.* that forecloses the argument that a **specific** teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) [available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf; and *KSR Guidelines Update* has been published in the Federal Register at 75 *Fed. Reg.* 53643-60 (Sep. 1, 2010) and is posted at USPTO's internet Web site at http://www.uspto.gov/patents/law/notices/2010.jsp]. The Examiner notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.,* the suggestion and motivation to combine Roth et al. (2000), Roth et al. (1996), and Starr et al. (2001) have been clearly set forth above in this office action.

It is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

3. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-

3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Primary Examiner
Art Unit 1632